REMARKS

I. Status of the claims

Claims 1-32 are pending in the application, and stand rejected. The Examiner has withdrawn claims 1-10 and 29-31 from consideration. Claim 11 is amended herewith, and claim 12 is canceled herein without prejudice.

II. Amendments to the claims

Claim 11 has been amended to recite that steps (b) and (c) are repeated for a total of two or more cycles. Support for this amendment can be found, for example, in claim 12 as filed, as well as in the examples described in the specification. No new matter has been added.

III. Rejections under 35 U.S.C. § 102(b)

A. Abra

The Examiner has rejected claims 11, 13-15, 17-18, 20, 22, 24-28 and 32 as being anticipated by U.S. Patent No. 6,126,966 to Abra et al. ("Abra"). The Examiner states that Abra's "method involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60-65 degrees. The liposomes were then extruded through filters an the temperature of liposomes at this state is 20-30 degrees." *Office Action* at p. 2. Applicants respectfully traverse.

To anticipate a claim under §102(b), a reference must teach each and every element of the claim, either expressly or inherently. M.P.E.P. § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union oil Co. of* California, 8144. F. 2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in

as complete detail as contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

Abra describes the preparation of a liposomal composition containing an entrapped cisplatin compound, where the liposomes are composed of a vesicle forming lipid and between 1-20 mole percent of a vesicle forming lipid derivatized with a hydrophilic polymer. *Abra* at col. 2, l. According to Abra, the hydrophilic polymer chains form a coating on both the inner and outer surfaces of the liposome, thereby improving stability of the liposome and extending blood circulation time of the liposomes. *Id* at col. 6, ll. 24-34. In forming the liposomes, Abra dissolves the lipids in warm ethanol (60-65° C), warms an aqueous solution of cisplatin to 63° C, and adds these solutions together "with the temperature of the mixture maintained at between 60-65° C." *Abra* at col. 9, ll. 51-65.

Abra does not disclose each and every element of the instant claims. In particular, Abra does disclose the steps of establishing the mixture at a first temperature and thereafter establishing the mixture at a second temperature for two or more cycles, as recited in amended claim 11. Rather, Abra specifies that the mixture is maintained at 60-65 °C. For at least reasons, Applicants respectfully request withdrawal of this rejection.

IV. Rejections under 35 U.S.C. § 103

A. Abra in view of Ye

The Examiner has rejected claims 12, 16, 19-23 as being obvious over Abra in view of U.S. Patent No. 5,998,899 to Ye et al. ("Ye"). The Examiner notes that Abra "lacks the repetition of the heating and cooling." *Office Action* at p. 3. Abra further notes that Abra does not teach the use of DPPC. *Id.* According to the Examiner, it would have been obvious "[t]o employ three cooling and

heating cycles in the method . . . of Abra . . . since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes." *Id.* Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528.

As discussed above, Abra maintains the mixture at 60-65 ° C, followed by diafiltration and dialysis, then extrusion. *Abra* at col. 9, l. 63 - col. 10, l. 4. Abra does not cool the liposomes to room temperature until after the extrusion step. *Id.* at col. 10, ll. 1-4. Ye describes a method for preparing liposomal formulations having increased encapsulation efficiency by increasing the number of carbons in the carbon chain at least one of the amphipathic lipids. *Ye* at col. 2, ll. 8-18. Ye does not disclose entrapment of any platinum compounds.

Applicants submit that the Examiner has not provided a "some articulated reasoning with some rational underpinning" for the skilled artisan to employ the temperature cycling of Ye, as

required under *KSR*. In particular, there is no reason for the skilled artisan to employ Ye's temperature cycling, which was used with PC's having 14-20 carbons, in a formulation comprising the hydrophilic polymer modified liposomes of Abra, which are modified with, for example, PEG chains of 500-10,000 Daltons, with any reasonable expectation of success. Nothing in the teachings of Ye suggest that temperature cycling would be facilitate drug equilibrium in a liposome comprising the hydrophilic polymer derived vesicles of Abra. For at least these reasons, Applicants respectfully request withdrawal of this rejection.

B. Yamauchi in view of Abra and Ye

The Examiner has rejected claims 11-28 as being obvious over U.S. Publication 2002/0182248 to Yamauchi ("Yamauchi"). The Examiner acknowledges that Yamauchi does not teach " the use of cisplatin as the drug and also repeating the steps of changing the temperature in two or more cycles." *Office Action* at p. 4. The Examiner contends that it would have been obvious to use cisplatin in the method of Yamauchi "since Yamauchi teaches that any drug can be encapsulated and . . . Abra shows the knowledge in the art of encapsulating cisplatin." *Id.* The Examiner further contends that it would have been obvious "[t]o employ three cooling and heating cycles . . . since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes." *Id.* at p. 4-5. Applicants respectfully traverse.

Yamauchi describes "liposomes and liposomal dispersions in which stability of drugs which have poor stability in the aqueous solution is improved." *Yamauchi* at ¶ 7. In particular, Yamauchi states that the stability of the aforementioned drugs becomes "markedly excellent when they are incorporated in liposomes prepared using a specified lipid," where the sphingolipid is "the main

component of the liposomal membrane." *Id.* at ¶ 8-9. Example 1 of Ye discloses the preparation of sphingolipid liposomes by adding an aqueous solution of PGE1 to evaporated sphingomyelin and heating to 60 °C. *Id.* at ¶ 57.

Applicants submit that the Examiner has not provided any "articulated reasoning with some rational underpinning" for the skilled artisan to use cisplatin in the sphingolipid liposomes of Yamauchi. Abra teaches encapsulation of cisplatin in liposomes comprising lipids specifically derivatized with hydrophilic polymer chains. The hydrophilic chains, according to Abra improve stability of the cisplatin and blood circulation. Abra's teachings provide no reasonable expectation of success for efficiently encapsulating cisplatin in the liposomes of Yamauchi. For at least this reason, the above reference combination fails to render the instant claims obvious.

Ye, which the examiner relies for disclosing three cycles of heating cooling, fails to remedy the deficiencies of Abra and Yamauchi. Specifically, Ye provides no teaching of encapsulating cisplatin. Additionally, nothing in Ye would provide any reasonable expectation of success in using the temperature cycling disclosed in Ye, which was applied to saturated and unsaturated PC's, to the sphingolipids of Yamauchi. For at least these reasons, Applicants respectfully request withdrawal of this rejection.

Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for

timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-006.01.**

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Respectfully submitted,

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